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Study protocol: a randomized controlled trial comparing the efficacy of open dialogue about complementary alternative medicine (OD-CAM) with standard care (SC) in improving quality of life in patients undergoing conventional oncology treatment (CAMONCO 2)

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Abstract

Introduction: Complementary alternative medicine (CAM) has been shown to reduce symptoms and side-effects and improve quality of life of patients undergoing conventional oncology treatment, but CAM might also cause symptoms and side-effects. Thus, patients need guidance towards safe and healthy use of CAM. According to published results, open dialogue about CAM (OD-CAM) between health professionals and patients as an integral part of anticancer treatment may improve patients' quality of life and well-being. Since the literature on the issue is sparse, the aim of this study is to assess the efficacy of OD-CAM integrated in conventional oncology care versus standard care (SC) in patients undergoing standard anticancer treatment.

Methods and analysis: Randomised controlled trial. Patients undergoing curative or palliative oncology treatment will be randomly assigned to SC with or without OD-CAM. A nurse specialist will facilitate the OD-CAM in one or two sessions. The primary endpoint is patient reported quality of life in relation to psychological well-being eight weeks after enrollment. Secondary endpoints are patient reported level of depression and anxiety, top concerns, and decision regret 8, 12 and 24 weeks after enrollment and overall survival.

Ethics and dissemination: According to the Committee on Health Research Ethics for Southern Denmark, ethics approval of this study is not required (S-20202000-5, 20/1019). The Region of Southern Denmark (Journal no. 20/11100) approved the storing and handling of data. The results of the study, whether positive, negative or inconclusive, will be disseminated through open-access, peer-reviewed publications, stake-holder-reporting and presentations at relevant conferences.

Trial registration: ClinicalTrails.gov, Identifier: NCT04299451 March 2020.

Strengths and limitations of this study

- The CAMONCO 2 study is the first randomised controlled trial to specifically assess the efficacy of OD-CAM on psychological quality of life and well-being and decisional as to conventional treatment. .
- The use of validated patient-reported questionnaires is a strength of the study.
- The use of the EORTC QLQ CAT CORE questionnaire increases measurement precision, flexibility, questions relevance to the individual patients, and reduces respondent burden.
- The complexity of the intervention makes it difficult to determine the potential effects.
- The pragmatic choice of including patients with different cancer diagnoses and prognoses may be too broad.

Introduction

An upward trend in patients' use of complementary and alternative medicine (CAM) (e.g. diet supplements, massage, acupuncture) as an adjunct to conventional oncology treatment and care is shown in several studies [1-9]. In the management of cancer-related symptoms and side effects CAM is relevant as supportive therapy e.g. acupressure and acupuncture reduce nausea and pain [10], aromatherapy alleviates sleep and anxiety disorders [11], and massage, yoga, mindfulness, and meditation have shown to increase quality of life (QoL) and reduce stress and fatigue [12]. It has also shown effect in relieving fear, fatigue, and depression [13] and enhancing hope [2], self-care, self-control, and empowerment [14, 15]. However, the level of evidence ranges from high to low, and some CAM treatments include a potential risk of interaction with conventional medicine [16-18]. Therefore, to ensure patient safety and high-quality care, interventions that include counselling and provision of CAM have been developed, tested and integrated in cancer centers [19-23]. Studies have shown that CAM counselling as an integral part of conventional oncology treatment increases patient engagement, patient-centred communication, and higher clinician [24] and patient satisfaction [25]. It addresses patient stress and uncertainty, reduces exposure to misleading information, and enhances the patient-physician relationship, which is paramount in delivering high-quality care [26]. Measurable clinically significant improvements on patients' main concerns and well-being has also been associated with CAM counselling when integrated in conventional oncology treatment [19]. The same applies to depression, anxiety, well-being, psychological distress and global distress (sum of pain, fatigue, nausea, depression) [27-30]. These studies however, are limited by the fact that

the elements of the CAM counselling were heterogeneous with no clear description, and the changes in symptoms, quality of life and well-being lack comparison with a control group. In a previous phase II randomized, controlled study including 112 patients and a qualitative interview of 15 patients (CAMONCO 1, ClinicalTrials.gov identifier NCT03857776, article in review), we developed and described the intervention 'open dialogue about CAM' (OD-CAM). Based on a person-centered and evidence based approach a specialist nurse guides the patient in safe and health promoting use of CAM. A detailed description is provided in Table 1. We tested the effects of OD-CAM on adverse events, quality of life (QoL), psychological well-being and perceived information. We found that OD-CAM does not increase the frequency and degree of side-effects and might contribute to reduced psychological stress and improve QoL. Based on the interviews, OD-CAM is likely to reduce uncertainty and decisional regret as to conventional oncology treatment. Although a tendency towards improved survival was observed, a study with greater statistical power is warranted in order to assess significant effects of OD-CAM. To our knowledge, the efficacy of OD-CAM integrated in conventional oncology care has not yet been investigated with specific focus on psychological well-being, QoL, decisional regret and survival.

Although there is an urgent need for interventions fulfilling patients` needs for guidance in safe and health promoting use of CAM, the evidence on conducting OD-CAM integrated in conventional oncology care is sparse. Sufficiently powered, randomized controlled trials are needed to explore the effects of OD-CAM integrated in conventional oncology care.

Aim

The primary aim of this randomized controlled study (CAMONCO 2) is to compare OD-CAM integrated in conventional oncology care with standard care in relation to psychological quality of life in patients undergoing conventional anti-cancer treatment. Secondary endpoints are the impact of OD-CAM on patient-reported level of depression, anxiety, and decision regret regarding conventional anti-cancer treatment, patient-reported concern and well-being and overall survival. Whether the attitude of the patients towards and/or use of CAM mediates the potential effect of OD-CAM will also be explored

Methods and analysis

Design

The CAMONCO 2 study is a randomized (1:1), controlled superior trial with two parallel groups investigating the efficacy of OD-CAM versus standard care in improving the QoL of patients undergoing anticancer treatment. Findings from the interviews in CAMONCO 1 indicated that potential effects of OD-CAM would not be identified right after the session; patients need time to consider and adopt the provided advice. The time of the primary outcome measure in the present study is therefore set at eight weeks after enrollment. CAMONCO 2 investigates patient-reported quality of life as opposed to side-effects, symptoms [31] and patient satisfaction [28-30]. Although the latter are important factors for patients with cancer, overall quality of life and survival is fundamental.

Setting

The study is conducted at the Oncology Outpatient Clinic, Vejle Hospital, University Hospital of Southern Denmark. The Department of Oncology offers

treatment and care to adult patients with breast, gynaecological, prostate, pulmonary, colorectal, anal, and pancreatic cancer**.** Annually, the number of outpatient visits amounts to 57,000 with 23,000 radiotherapy fractions and 9,300 chemotherapy and immunotherapy treatments administered.

Participants

Adult patients diagnosed with primary cancer or recurrence within the last three months are offered enrolment. The inclusion criteria include planned antineoplastic treatment for at least two months and a life expectancy of six months or more. Patients participating in other trials interfering with the intervention or data collection are not eligible.

Procedure

Recruitment

Potential candidates are identified and screened for initial eligibility by nurse coordinators according to the inclusion and exclusion criteria. In connection with initial cycles of chemotherapy, immunotherapy, and/or antibody therapy in the outpatient clinic eligible patients are informed and invited to participate in the study by a trained nurse or study nurse. Eligible patients are provided with written and oral information about the study objectives, and signed consent is obtained from those willing to participate. Consent must be given within 12 weeks from treatment start, i.e. at the fourth cycle of treatment at the latest. Recruitment continues until the defined sample size is reached. For optimization of the selection bias analysis, patients declining to participate will be encouraged to complete a questionnaire on sex, age, type of cancer and treatment purpose (curative or palliative).

Randomisation

Upon signed consent patients complete baseline questionnaires on demographic data, cancer diagnosis and stage, oncology treatment, quality of life, degree of anxiety and depression, two top concerns, decision regret as to anticancer treatment and their attitude towards and possible use of CAM. Randomization is subsequently performed by the clinical trial unit using OPEN Randomize (https://open.rsyd.dk/), an online central randomization service. Patients are randomized 1:1 to the intervention and control groups with no further stratification. OPENs Randomize ensures allocation concealment, as it will not release the randomization code until the patient has been enrolled in the study, which takes place when all baseline measurements have been completed.

Blinding

The principal investigator is blinded to the allocation and not involved in the treatment and care of the patients. Due to the nature of the intervention, participants and staff cannot be blinded to the allocation, but patients are strongly encouraged not to disclose their allocation status at the follow-up visits. Results data are entered in separate sheets allowing for analysis without revealing allocation status. All statistical analyses will be performed blinded to group allocation and results will be interpreted prior to disclosure.

Interventions

Eligible patients are randomized in equal proportions between OD-CAM and standard care (SC) and SC with referral to www.kabcancer.dk

Intervention group: OD-CAM

In addition to standard care (SC), patients in the intervention group will participate in one or two sessions on OD-CAM facilitated by a nurse-specialist, who has completed the program Fellowship in Integrative Medicine at The University of Arizona, USA. This is a training program for health professionals in empowering individuals and communities to optimize health and well-being through evidence-based, sustainable and integrative approaches [32]. Inspired by the principles of Integrative Medicine, the nurse-specialist pays careful attention to the patients' experiences, values, beliefs, concerns and needs and provides evidence based information as to which CAM treatments are recommendable or should be avoided. A primary caregiver may participate, if preferred by the patient. The number of OD-CAM sessions depends on the individual patient. The nurse does not offer CAM treatments. The guideline for OD-CAM presented in Table 1 is inspired by the Andrew Weil Center for Integrative Medicine, University of Arizona and Schofield et al.'s recommendations [32, 33].

Table 1. Guideline for Open Dialogue about Complementary Alternative Medicine (OD-CAM)

Setting	
Preparation	The patient is asked to prepare for the session, including considerations as to current and future use of CAM
Environment	The OD-CAM takes place in a consultation room designed specifically to provide a healing environment with soft and natural lighting, flowers, and relaxing furniture. The room is separate from the clinic.
Schedule	The OD-CAM must be conducted no later than two weeks after randomization and scheduled to last 60 minutes
Nurse specialist	The nurse specialist has completed the program Fellowship in Integrative Medicine at the University of Arizona. This is a training program for health professionals in

	empowering individuals and communities to optimize health and well-being through evidence-based, sustainable and integrative approaches
Integrative	Integrative includes a healing oriented approach viewing and respecting patients as whole and unique physical, emotional, social and spiritual beings with values, knowledge, preferences and beliefs. It aims to optimize health, quality of life, clinical outcomes, and support patients to become active participants in their own healing and health. It emphasizes the therapeutic relationship between health professional and patient. Based on evidence, CAM-information is provided alongside conventional cancer treatment.

Content	In collaboration with the patient	Examples of questions to ask
1. Understand	Elicit the patients' understanding of their situation. Clarify information preferences before asking about CAM use. Ask open questions focusing on psychological/existential issues.	What is your understanding of the situation at this point? What concerns you most about your illness and treatment? What are your hopes for the future?
2. Respect	Respect cultural, linguistic and belief diversity. Awareness of attitudes and information needs in relation to models of illness and treatment	What do you believe might have caused your illness?
3. Ask	Ask questions about CAM use. Adopt an inquisitive, open minded and non-judgmental approach.	Are you currently doing or considering doing anything else for your condition/side effects, your overall health or well-being? Are you taking any other medications or treatments?

	Clarify reasons for asking about CAM.	It is very important for me to know about any initiatives you have taken to address your illness so I can help you the best way possible. I am not an expert in this (CAM) but it is important to make sure that any actions or medications you take do not interact negatively with the treatment we give you.
4. Explore (if the patient is already /considering using CAM)	Explore the details of CAM use and actively listening. Enquire about current and considered CAM use	Can you tell me more about this CAM, please? What does it involve? How often do you use it? Have you used it before?
	Ask about reasons for and expected outcomes of CAM use.	What are your reasons for using this CAM? What are you hoping for from this CAM? Has it been helpful so far? How will you know it is helpful for you?
	Ask about expected outcomes of conventional treatment.	
	Ask if there is a provider of the CAM (if relevant), who it is and what their role will be in relation to the CAM use.	Who are you seeing for this CAM? (if relevant)
	Explore the evidence for the CAM's efficacy and safety.	Do you know if there has been any research on the effect of this CAM?
	Provide balanced evidence advice in relation to the CAM.	
	Help respond to advice from family and friends (if relevant).	Others want the best for you. Let´s talk about these suggestions. What do you think of these suggestions?

5. Respond	Respond to the patient's emotional state, encourage expression of feelings Express empathy. Support the desire for hope and control; address issues the patient seeks to influence by using CAM (e.g. symptom control, alleviation of side-effects, control, desire to live longer)	How are you feeling emotionally? How are you coping with your situation? It sounds like you want to do everything possible. It is natural to feel a need to explore the possible options and I fully support you in that (if relevant)
6. Discuss	Discuss relevant concerns about CAM while respecting the patient's beliefs. Possible concerns: – caution about substances with unknown effect and quality – high financial or time cost for CAM of unknown benefits – potential for psychological harm Discuss a reasonable trial period over which an assessment can be made regarding benefits/efficacy of CAM. A symptom diary may help determine whether the CAM is beneficial for the individual patient. Explore alternative ways of addressing the patients	I believe there is little evidence about the benefit or harm associated with this CAM. Therefore, we should be cautious. Might the time involved prevent you from doing other things you like to do? How do you think you might feel if you followed this advice (CAM use) but did not achieve the outcome you hoped for? How long would you expect it to take to see a benefit from this CAM? I can see that you hope this CAM will help you/your cancer/symptoms/side effects/well-being.

		underlying needs, hopes or fears (especially if there are concerns about potential harms of the CAM)	There are other options we can look at, too. Would you like to hear about them?
7.	**Advise**	Encourage use of CAM that may be beneficial.	I recommend this CAM, The evidence suggests that it could help you.
		Accept use of CAM for which there is no evidence of physical harm or benefit. Support the decision, even though it conflicts with your private view.	We do not know much about this CAM, but it does not seem to be harmful and it may even help you. I respect that this is what you wish to do.
		Discourage use of CAM where there is no good evidence. It will be unsafe or harmful.	I have to be honest with you. I am concerned that this CAM may do you greater harm than good.
		Particularly, discourage use of unproven CAM if it is to be used in place of potentially beneficial treatment, especially potentially curative treatment.	I respect and support your right to make this decision. However, I firmly believe that you have a better chance of a good outcome if you follow this treatment plan. While there is little evidence for us to know if this CAM will be helpful, of course the decision is yours.
		Balance advice with an acknowledgement of the patient's rights for self-determination and autonomy.	
8.	**Summarize**	Summarize main points of discussion and check patient's understanding.	We have covered a lot today. Just so that I can check that I have explained things properly, can you summarize what we have discussed?
		Provide websites and other information or resources, e.g.	Do you have any further questions or issues you would like to discuss?

		information about supplements, dietary, breathing exercises, yoga, meditation, etc.	
9.	**Document**	Document the discussion in the patient's medical record and send a copy to the patient.	I will document what we have discussed today in your medical record and we will send a copy to your secure inbox.
10.	**Follow-up**	Follow-up discussion about CAM if relevant	

Control group: SC

Patients randomized to the control group receive SC i.e. oncology treatment and care, including antineoplastic drugs. SC also involves continuous assessment of performance status, side effects, symptoms, and their management by specialist doctors and nurses. The patients are given a pamphlet describing and referring to www.kabcancer.dk, a website developed by a team of researchers. Based on systematic reviews, it presents information on potential effects and outcomes of specific CAM treatments such as acupuncture, antioxidant supplements, mindfulness, herbs, massage etc. [34].

Primary outcome measure

The primary outcome measure is the difference in level of patient reported quality of life, specifically with regard to emotional well-being, between the two groups eight weeks^{t1} after enrollment. The patient reported data will be registered according to the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire computerized adaptive test (EORTC QLQ CAT Core). The EORTC QLQ CAT core is a translated and validated instrument,

which encompasses 15 domains with pools of validated questions. Within each pool of questions, the EORTC CAT Core selects and presents the question that is the most informative for the individual patient. The instrument lists questions assessing quality of life, including functional scales, symptom scales, global health status, and psychosocial scales [35].

Secondary outcome measures

The secondary outcome measure is the change from baseline to post intervention 8^{t1}, 12^{t2} and 24^{t3} weeks after enrollment. Difference between the two groups will be assessed in the following outcomes.

- Patient reported anxiety and depression evaluated by the Hospital Anxiety and Depression Scale (HADS). HADS is a translated and validated self-assessment questionnaire detecting states of anxiety and depression in the setting of hospital outpatient clinics [36].
- Patient reported level of top concern evaluated by Measure Yourself Concerns and Wellbeing (MYCaW). MYCaW is an individualized questionnaire scoring patients concerns, problems and well-being and collecting qualitative data about other major events in a patients` life and what has been most important to the patient [37].
- Patient-reported level of decision regret regarding conventional oncology treatment evaluated by the Decision Regret Scale (DRS). The DRS is a validated measurement tool measuring the distress or remorse after a health care decision [38].
- Patient-reported quality of life 12 and 24 weeks after enrollment evaluated by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ CAT Core) [35].

- Overall survival

Process measures

Variables likely to mediate the effect of OD-CAM will be measured twice during follow-up (at baseline^{-t1} and 24^{t3} weeks):

- Attitude of CAM
- Use of CAM including type

Flowchart and participant time line are presented in Table 2 and Figure 1, respectively.

Table 2 Participant timeline

	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		
TIMEPOINT	$-t_1$	0	t_1	t_2	t_3
ENROLLMENT					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS					
SC+OD-CAM			◆———	———	———◆
SC			◆———	———	———◆
ASSESSMENTS					
Baseline variables:					
Demographic data	X				
QoL	X				
Anxiety and depression	X				
Top concerns	X				
Decision regret	X				
Attitude and use of CAM	X				
Outcome variables:					
QoL			X	X	X
Anxiety and depression			X	X	X
Top concerns			X	X	X
Decision regret			X	X	X
Mediators:					
Attitude and use of CAM					X

Insert Figure 1 Flowchart

Data management

Cooperation and a license agreement have been established with the OPEN organization (Odense Patient data Explorative Network). All sensitive data will be registered and stored in OPEN Analyze and handled in REDCap, a mature, secure web application for building and managing online surveys and databases.

REDCap provides logging at the transaction level and may therefore store and process any person identifiable data. Thus, congruent with guidelines, sensitive data about the patients are stored and handled securely [39].

STATA software (Texas, USA) will be used as a platform for statistical analysis. Since STATA only provides logging at the file level, participant data will be pseudonymized by assigning a unique ID number to each participant. The list of ID numbers and the pertaining key will be kept separately. Information on user and time of data processing in STATA will be logged.

Only persons involved in the project are allowed to access data. In accordance with the license agreement principal investigator (Mette Stie) controls access and rights and the OPEN data manager provides the access.

Research nurses in the clinical trial unit will only have the right to enter data into REDCap. Data collected on paper (baseline data) will be registered in REDCap. The electronic questionnaires are completed by the patients directly in REDCap, which promotes data quality.

Statistical plan

Sample size

The sample size is calculated on the basis of the primary endpoint. A 10-point difference or more in the quality of life EORTC QLQ CAT Core scale from baseline to 8 weeks between the two study groups is considered of clinical importance. We plan a randomized controlled study of a continuous response variable in independent control and experimental subjects with one control per experimental subject. In a previous study, the response within each subject group was normally distributed with a standard deviation of 24.2. If the true difference in the experimental and control means is 10, the number of subjects required in each group is 93 to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.8. The type I error probability associated with this test of the null hypothesis is 0.05. With an expected loss of 10% the total number of patients to be enrolled is 207.

Statistical methods

The intervention arm (OD-CAM) will be compared against the control arm (SC plus referral to www.kabcancer.dk) in all primary analyses. Demographic data will be presented as counts (n) and proportions (%), respectively, means and standard deviations (SD) with 95% confidence intervals (CI). Chi-square test or a Fisher exact test will be applied where appropriate to detect differences between the two groups in relation to quality of life. The EORTC QLQ CAT Core, HADS scores, DRS, and MYCaW will be reported as means and standard deviations compared between the two groups by using Student's t-test or Mann Whitney's U test, depending on normality of the data checked by quantile-quantile plots.

P-values will be reported to three decimal places with p-values less than 0.001 reported as <0.001. Two-sided p-values with a 0.10 level of significance will be used for all tests. A professional academic, statistician blinded to the study group assignment will conduct all analyses. For potential subgroup analyses, appropriate regression methods will be applied.

Patient and public involvement

The Patient and Relative Council Board at Lillebaelt Hospital initiate the CAMONCO 1 and 2 studies. Before submission, this research protocol was developed and reviewed by the CAMONCO steering group, a joint initiative of patients with cancer, health professionals and staff representing medical oncology, oncology nursing and nurse managers. Furthermore, Danish Cancer Society is represented in the CAMONCO steering group. Patients in the CAMONCO steering group were in particular involved in development of the intervention OD-CAM and time required to participate in the study. Also, patients` priorities, experiences and preferences informed some of the outcome measures (EORTC-CAT core and MYCaW). The steering group will continuously provide feedback on interim findings and advise on dissemination of results and output of the study. Patients from the steering group are pivotal partners in the dissemination of the CAMONCO 1 and 2 studies to relevant stakeholders.

Ethics and disseminations

Patients are informed about the purpose of the study, including the right to withdraw, the guarantee of anonymity, and the confidentiality of the data. Trained nurses or study nurses will introduce and discuss the trial with the patients. If needed, patients will be able to have an informed discussion about the trial with

the principal investigator. The trained nurses or study nurses will obtain written consent from patients willing to participate in the trial. Subsequently, demographic data and questionnaires regarding patients' quality of life, depression and anxiety, concerns and wellbeing, and decision regrets will be collected, preserved and shared only by researchers involved in this trial.

It is estimated that the study does not involve any risk to the patients, and the potential benefits clearly outweigh the theoretical risks involved in participating in open dialogue about CAM and completing questionnaires.

The results of the study, whether positive, negative or inconclusive, will be published in a relevant journal with authorship following the Vancouver rules.

The procedures in this study adhere to the principals of the Declaration of Helsinki.

Discussion and conclusion

The need for OD-CAM as an integral part of oncology care becomes increasingly urgent with the increasing number of patients using CAM as an adjunct to conventional oncology treatment. To the best of our knowledge, this is the first randomized controlled study that aims to evaluate the efficacy of OD-CAM integrated in conventional oncology care versus standard care in patients undergoing anti-cancer treatment, by the EORTC QLQ CAT Core, the HADS, the MYCaW and the DRS questionnaires. The current study will shed light on the effect of OD-CAM on patients receiving outpatient oncology treatment for cancer and provide foundation for guidelines on how to meet patients` needs for guidance in safe and health promoting use of CAM. It will also add to the evidence-based knowledge on communication about CAM between patients and health professionals in clinical practice. Only few studies have exclusively explored the

effects OD-CAM integrated in conventional oncology care [25]. Most of them include both open dialogue and the provision of CAM and mainly assess patient satisfaction. According to our knowledge, only one study other than our previous trial (CAMONCO 1), has investigated the effects of open dialogue about CAM on patients' symptoms, quality of life and well-being [31]. The present CAMONCO 2 study will therefore be an important contribution to the sparse knowledge on the issues as integrated in conventional oncology care.

Strengths and limitations

One limitation of the present study may be that since little is known about the effects of OD-CAM, the pragmatic choice of including patients with different cancer diagnoses and prognoses may be too broad. On the other hand, these patients have much in common including the need for self-care, self-control, and empowerment, which are some of the main reasons for using CAM [40-42]. The randomization secures the even distribution of different diagnoses and prognoses. Only the researchers are blinded to the allocation, which is a limitation but necessary due to the nature of the intervention. The complexity of the intervention also makes it difficult to determine the potential effects, but the same nurse-specialist conducts the OD-CAM throughout the study, which secures a homogenous intervention.

The prospective, randomized design with a control group and the use of validated patient-reported questionnaires is a strength of the study. Strengths also include the use of the EORTC QLQ CAT CORE questionnaire, it increases measurement precision, flexibility, question relevance to the individual patients, and reduces respondent burden.

Figure legends

Figure 1 flowchart is a flowchart showing the study-schedule of enrolment, interventions, and assessments.

Declarations

Author contributions

All authors contributed to the study conception and design. Mette Stie and Lars Henrik Jensen will perform material preparation, data collection and analysis. Mette Stie wrote the first draft of the manuscript and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Competing interest statements

The authors declare that they have no competing interest.

Consent for publication

Not applicable

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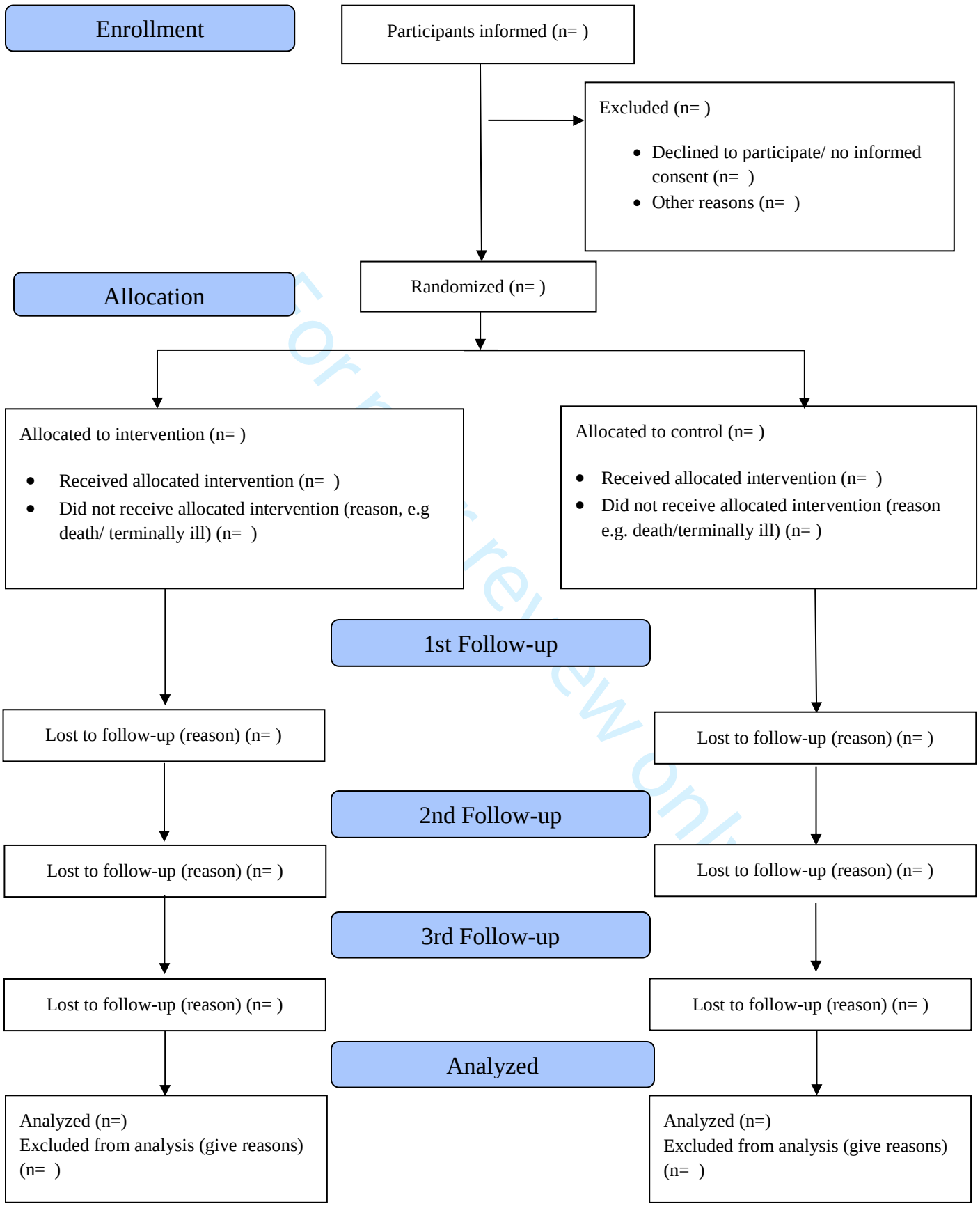
Figure 1 Flow chart



SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym : **Study protocol: a randomized controlled trial comparing the efficacy of open dialogue about complementary alternative medicine (OD-CAM) with standard care (SC) in improving quality of life in patients undergoing conventional oncology treatment (CAMONCO 2)**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry: **Trial registration: ClinicalTrails.gov, Identifier: NCT04299451 March 2020.**
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier: **OK**
Funding	4	Sources and types of financial, material, and other support: **Declarations - *Funding* page 15**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **Declarations- *Author contributions* page 15**
	5b	Name and contact information for the trial sponsor: **Lars Henrik Jensen, Consultant Oncologist, Clinical Associate Professor, PhD, Department of Oncology, Vejle Hospital, University Hospital of Southern Denmark, Beriderbakken 4, 7100 Vejle. Direct tel.: +45 79406802**

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities. **The Idella Foundation has no role in study design, collection, management, analysis and interpretation of data; writing of the report and the decision to submit the report for publication. They have no authority over any of the above activities.**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) **N/A**
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **Described in the Background section at page 3**
	6b	Explanation for choice of comparators **Background page 3-4**
Objectives	7	Specific objectives or hypotheses **Aim page 5**
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **Design page 5**
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **Setting page 5-6**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **Participants page 6**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **Interventions page 7-8**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease**) It is estimated that the study does not involve any risk to the patients, and the potential benefits clearly outweigh the theoretical risks involved in participating in open dialogue about CAM and completing questionnaires – see Ethical considerations page 12**

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **If questionnaires are not completed within 2 weeks a reminder is sent**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **Yes**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **Primary and secondary outcome measures are describe at page 9-10. Clinical relevance is described in Design page 5**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) **see Figure 1 and Table 2**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **Statistical plan page 11**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **Recruitment page 6**

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions. **Upon signed consent and completed baseline questionnaires randomization is performed by the clinical trial unit using OPEN Randomize (https://open.rsyd.dk/), an online central randomization service. Page 7**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **–do- page 7**

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions**. Recuitment procedures and allocation is described in the recruitment and the randomization section p. 6 and 7, respectively.**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how. **The principal investigator is blinded to the allocation –see Blinding section page 7**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **n/a**

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **Questionnaires are described in the Primary outcome and secondary outcome section page 9-10 , Data management page 10-11**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **Data management page 10-11**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **Data management procedures are described in the protocol and in the Data management section page 10-11**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **Statistical plan page 11-12**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **N/A**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **N/A**

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **N/A**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **N/A**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **N/A**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **N/A**
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval Declarations. **See Ethics approval page 14**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **n/a**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **See Ethical considerations page 12**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **N/A**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial **See Data management page 10 and Ethical considerations page 12**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site. **No competing interest**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators. **Only researchers involved in this project will have access to final trial dataset**.
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **N/A**

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **The results of the study, whether positive, negative or inconclusive, will be published in a relevant journal with authorship following the Vancouver rules.**
	31b	Authorship eligibility guidelines and any intended use of professional writers **N/A**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **N/A**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Efficacy of open dialogue about complementary and alternative medicine compared with standard care in improving quality of life in patients undergoing conventional oncology treatment (CAMONCO 2): protocol for a randomized controlled trial

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Efficacy of open dialogue about complementary and alternative medicine compared with standard care in improving quality of life in patients undergoing conventional oncology treatment (CAMONCO 2): protocol for a randomized controlled trial

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Abstract

Introduction: Complementary alternative medicine (CAM) has been shown to reduce symptoms and adverse effects and improve quality of life of patients undergoing conventional oncology treatment, but CAM might also cause symptoms and adverse effects such as headache and fatigue. Thus, patients need guidance towards safe and healthy use of CAM. According to published results, open dialogue about CAM (OD-CAM) between health professionals and patients as an integral part of anticancer treatment may improve patients' quality of life and well-being. Since the literature on the issue is sparse, the aim of this study is to assess the efficacy of OD-CAM integrated early in conventional oncology treatment versus standard care (SC) in patients undergoing standard anticancer treatment.

Methods and analysis: The study is a randomized controlled trial, being conducted at an oncology outpatient clinic in Denmark. 207 patients undergoing curative or palliative oncology treatment for breast, gynaecological, prostate, pulmonary, colorectal, anal, or pancreatic cancer will be randomly assigned to SC with or without OD-CAM. A nurse specialist will facilitate the OD-CAM in one or two sessions. The primary endpoint is patient reported quality of life in relation to psychological well-being eight weeks after enrollment. Secondary endpoints are patient reported level of depression and anxiety, top concerns, and decision regret 8, 12 and 24 weeks after enrollment, and overall survival.

Ethics and dissemination: According to the Committee on Health Research Ethics for Southern Denmark, ethics approval of this study is not required (S-20202000-5, 20/1019). The Region of Southern Denmark (Journal no. 20/11100) approved the

storing and handling of data. Participants' informed consent will be obtained before inclusion and randomization. The results of the study, whether positive, negative or inconclusive, will be disseminated through open-access, peer-reviewed publications, stake-holder-reporting and presentations at relevant conferences.

Trial registration: ClinicalTrails.gov, NCT04299451 (March 2020).

Strengths and limitations of this study

- The CAMONCO 2 study is the first randomized controlled trial to specifically assess the efficacy of OD-CAM on psychological quality of life and well-being and decisional as to conventional treatment.
- The use of validated patient-reported questionnaires is a strength of the study.
- The use of the EORTC QLQ CAT CORE questionnaire increases measurement precision, flexibility, questions relevance to the individual patients, and reduces respondent burden.
- The complexity of the intervention makes it difficult to determine the potential effects.
- The pragmatic choice of including patients with different cancer diagnoses and prognoses may be too broad.

Introduction

An upward trend in patients' use of complementary and alternative medicine (CAM) as an adjunct to conventional oncology treatment and care is shown in Denmark [1, 2] and internationally [3-8]. The term CAM refers to therapies such as acupuncture, meditation, herbs and dietary supplements used as a supplement to conventional

cancer treatment [9]. A cross-sectional descriptive survey with 956 patients from 14 different European countries including Denmark has shown that herbs together with homeopathy, vitamins/minerals, medicinal teas, spiritual therapies and relaxation techniques are the most commonly used CAM modalities among patients with cancer [10]. In the management of cancer-related symptoms and adverse events of conventional oncology treatment CAM is relevant as supportive therapy. Acupressure and acupuncture have been shown to reduce nausea and pain [11], aromatherapy alleviates sleep and anxiety disorders [12], and massage, yoga, mindfulness, and meditation have been shown to increase quality of life (QoL) and reduce stress and fatigue [13]. CAM may also relieve fear, fatigue, and depression [14] and enhance hope [4], self-care, self-control, and empowerment [15, 16]. The level of evidence, however, ranges from high to low, and some CAM modalities include risk of interaction when combined with conventional oncology treatment [17-19]. To ensure patient safety and high-quality care some cancer centers thus practice integrative oncology [20-24]. Integrative oncology is a patient-centred, evidence-informed field of cancer care that utilizes mind and body practices, natural products, and/or lifestyle modifications from different traditions alongside conventional cancer treatments. The fundamental starting point of integrative oncology is that patients and health professionals openly discuss safe and healthy use of CAM [9]. Studies have shown that counselling about CAM as an integral part of conventional oncology treatment engages patients in their own health care, increases patient-centred communication, and leads to higher clinician [25] and patient satisfaction [26]. Counselling about CAM also addresses patient stress and uncertainty because it reduces exposure to misleading information. Furthermore, it enhances the patient-physician relationship,

which is essential in delivering high-quality care [27]. Measurable clinically significant improvements on patients' main concerns and well-being has also been associated with CAM counselling when integrated in conventional oncology treatment [20]. Improvements in relation to depression, anxiety, well-being, psychological distress and global distress (sum of pain, fatigue, nausea, depression) have also been identified [28-31]. These studies, however, are limited by the fact that the elements of the CAM counselling were heterogeneous with no clear description, and the changes in symptoms, quality of life and well-being lack comparison with a control group. In a previous phase II randomized, controlled study including 112 patients and a qualitative interview of 15 patients (The CAMONCO 1 study) [32], we developed and described the intervention 'open dialogue about CAM' (OD-CAM). Based on a person-centered and evidence based approach a specialist nurse guides the patient in safe and health promoting use of CAM. The OD-CAM is conducted early in the conventional oncology treatment trajectory. A detailed description is provided in Table 1. We tested the effects of OD-CAM on adverse events of conventional cancer treatment, quality of life (QoL), psychological well-being and perceived information. We found that OD-CAM does not increase the frequency and degree of adverse events of conventional cancer treatment and might contribute to reduced psychological stress and improve QoL. Based on data from the interview study, the participants found that OD-CAM was beneficial for reducing uncertainty and decisional regret as to conventional oncology treatment. Although a tendency towards improved survival was observed, a study with greater statistical power is warranted in order to assess significant effects of OD-CAM. To our knowledge, the efficacy of OD-CAM integrated early in the conventional oncology treatment trajectory has not

yet been investigated with specific focus on psychological well-being, QoL, decisional regret and survival.

Although there is an urgent need for interventions fulfilling patients` needs for guidance in safe and health promoting use of CAM, the evidence on conducting OD-CAM integrated in conventional oncology care is sparse. Sufficiently powered, randomized controlled trials are needed to explore the effects of OD-CAM integrated in conventional oncology care.

Aim

The overall hypothesis of this study is that patients newly diagnosed with a primary cancer or a recurrence of cancer will benefit from OD-CAM that is integrated early in the conventional oncology treatment trajectory. The primary aim of this randomized controlled study (CAMONCO 2) is to compare OD-CAM integrated early in the conventional oncology treatment trajectory with standard care in relation to psychological quality of life in patients undergoing conventional anti-cancer treatment. Secondary endpoints are the impact of OD-CAM on patient-reported level of depression, anxiety, and decision regret regarding conventional anti-cancer treatment, patient-reported concern and well-being and overall survival. Whether the attitude of the patients towards and/or use of CAM mediates the potential effect of OD-CAM will also be explored.

Methods and analysis

Design

The CAMONCO 2 study is a randomized (1:1), controlled superior trial with two parallel groups investigating the efficacy of OD-CAM versus standard care in improving the QoL of patients undergoing anticancer treatment. There is no consensus in the literature of which time point a potential effect of OD-CAM will be identified. However, data from the interview study in CAMONCO 1 indicated that participants did not experience the benefits of OD-CAM right after the OD-CAM session; they need time to consider and adopt the provided advice about CAM. The time of the primary outcome measure in the present study is therefore set at eight weeks after enrollment. CAMONCO 2 investigates patient-reported quality of life as opposed to adverse events of conventional cancer treatment and, cancer-related symptoms [33] and patient satisfaction [29-31]. Although the latter are important factors for patients with cancer, overall quality of life and survival is fundamental.

Setting

The study is conducted at the Oncology Outpatient Clinic, Vejle Hospital, University Hospital of Southern Denmark. The Oncology Outpatient Clinic offers conventional treatment and care to adult patients with breast, gynaecological, prostate, pulmonary, colorectal, anal, and pancreatic cancer**.** Annually, the number of outpatient visits amounts to 57,000 with 23,000 radiotherapy fractions and 9,300 chemotherapy and immunotherapy treatments administered. In Denmark, CAM is not a part of the official health care system. CAM is practiced outside the official health care system and paid out of pocket.

Participants

Adult patients aged ≥18 years, diagnosed with primary cancer or recurrence within the last three months are offered enrolment. The inclusion criteria include planned antineoplastic treatment for at least two months. Life expectancy of six months or more and signed informed consent are also criteria for inclusion. Patients that participate in other trials that interfere with the intervention or data collection will be excluded.

Procedures

Recruitment

Nurse coordinators identify and screen potential candidates for initial eligibility according to the inclusion and exclusion criteria. In connection with initial cycles of chemotherapy, immunotherapy, and/or antibody therapy in the outpatient clinic eligible patients are informed and invited to participate in the study by a trained nurse or study nurse. Eligible patients are provided with written and oral information about the study objectives procedures. Signed consent is obtained from those willing to participate. Consent must be given within 12 weeks from treatment start, i.e. at the fourth cycle of treatment at the latest. Recruitment continues until the defined sample size is reached. For optimization of the selection bias analysis, patients declining to participate will be encouraged to complete a questionnaire on sex, age, type of cancer and treatment purpose (curative or palliative).

Randomization

Upon signed consent patients, complete baseline questionnaires on demographic data, cancer diagnosis and stage, oncology treatment, quality of life, degree of anxiety and

depression, two top concerns, decision regret as to anticancer treatment and their attitude towards and possible use of CAM. The clinical trial unit using OPEN Randomize (https://open.rsyd.dk/), an online central randomization service, subsequently performs randomization. Patients are randomized 1:1 to the intervention and control groups with no further stratification. OPENs Randomize ensures allocation concealment, as it will not release the randomization code until the patient has been enrolled in the study. Thus, randomization will be performed when all baseline measurements have been completed.

Blinding

This is a non-blinded study. Neither participants nor staff can be blinded to the allocation due to the nature of the intervention. The principal investigator is blinded to the allocation and not involved in the treatment and care of the patients. Results data are entered in separate sheets allowing for analysis without revealing allocation status. All statistical analyses will be performed blinded to group allocation and results will be interpreted prior to disclosure.

Interventions

Eligible patients are randomized in equal proportions between OD-CAM and standard care (SC) and SC with referral to www.kabcancer.dk

Intervention group: OD-CAM

OD-CAM has been developed and described in our previous study (CAMONCO 1) [32]. As in CAMOCO 1, patients in the intervention group will receive standard care (SC) and participate in one or two sessions on OD-CAM facilitated by a nurse-

specialist, who has completed the program Fellowship in Integrative Medicine at The University of Arizona, USA. This program trains health professionals in empowering individuals and communities to optimize health and well-being through evidence-based, sustainable and integrative approaches [34]. In the OD-CAM, the nurse-specialist is inspired by the principles of Integrative Medicine. Based on the patients' individual experiences, values, beliefs, concerns and needs, the nurse-specialist provides evidence-based information as to which CAM modalities are recommendable or should be avoided. A primary caregiver may participate, if preferred by the patient. The number of OD-CAM sessions depends on the individual patient. The OD-CAM is exclusively a dialogue between the nurse-specialist and the patient. The nurse-specialist does not offer CAM treatments. The guideline for OD-CAM is presented in Table 1, and was developed in our previous study (CAMONCO 1)[32]

Table 1. Guideline for Open Dialogue about Complementary Alternative Medicine (OD-CAM)

Setting	
Preparation	The patient is asked to prepare for the session, including considerations as to current and future use of CAM
Environment	The OD-CAM takes place in a consultation room designed specifically to provide a healing environment with soft and natural lighting, flowers, and relaxing furniture. The room is separate from the clinic.
Schedule	The OD-CAM must be conducted no later than two weeks after randomization and scheduled to last 60 minutes
Nurse specialist	The nurse specialist has completed the program Fellowship in Integrative Medicine at the University of Arizona. This is a training program for health professionals in

	empowering individuals and communities to optimize health and well-being through evidence-based, sustainable and integrative approaches
Integrative	Integrative includes a healing oriented approach viewing and respecting patients as whole and unique physical, emotional, social and spiritual beings with values, knowledge, preferences and beliefs. It aims to optimize health, quality of life, clinical outcomes, and support patients to become active participants in their own healing and health. It emphasizes the therapeutic relationship between health professional and patient. Based on evidence, CAM-information is provided alongside conventional cancer treatment.

Content	In collaboration with the patient	Examples of questions to ask
1. Understand	Elicit the patients' understanding of their situation. Clarify information preferences before asking about CAM use. Ask open questions focusing on psychological/existential issues.	What is your understanding of the situation at this point? What concerns you most about your illness and treatment? What are your hopes for the future?
2. Respect	Respect cultural, linguistic and belief diversity. Awareness of attitudes and information needs in relation to models of illness and treatment	What do you believe might have caused your illness?
3. Ask	Ask questions about CAM use.	Are you currently doing or considering doing anything else for your condition/adverse effects, your overall health or well-being?

	Adopt an inquisitive, open minded and non-judgmental approach. Clarify reasons for asking about CAM.	Are you taking any other medications or treatments? It is very important for me to know about any initiatives you have taken to address your illness so I can help you the best way possible. I am not an expert in this (CAM) but it is important to make sure that any actions or medications you take do not interact negatively with the treatment we give you.
4. Explore (if the patient is already /considering using CAM)	Explore the details of CAM use and actively listening. Enquire about current and considered CAM use Ask about reasons for and expected outcomes of CAM use. Ask about expected outcomes of conventional treatment. Ask if there is a provider of the CAM (if relevant), who it is and what their role will be in relation to the CAM use. Explore the evidence for the CAM's efficacy and safety. Provide balanced evidence advice in relation to the CAM.	Can you tell me more about this CAM, please? What does it involve? How often do you use it? Have you used it before? What are your reasons for using this CAM? What are you hoping for from this CAM? Has it been helpful so far? How will you know it is helpful for you? Whom are you seeing for this CAM? (if relevant) Do you know if there has been any research on the effect of this CAM?

	Help respond to advice from family and friends (if relevant).	Others want the best for you. Let´s talk about these suggestions. What do you think of these suggestions?
5. Respond	Respond to the patient's emotional state, encourage expression of feelings	How are you feeling emotionally? How are you coping with your situation?
	Express empathy.	It sounds like you want to do everything possible.
	Support the desire for hope and control; address issues the patient seeks to influence by using CAM (e.g. symptom control, alleviation of adverse effects, control, desire to live longer)	It is natural to feel a need to explore the possible options and I fully support you in that (if relevant)
6. Discuss	Discuss relevant concerns about CAM while respecting the patient's beliefs. Possible concerns: – caution about substances with unknown effect and quality – high financial or time cost for CAM of unknown benefits – potential for psychological harm	I believe there is little evidence about the benefit or harm associated with this CAM. Therefore, we should be cautious. Might the time involved prevent you from doing other things you like to do? How do you think you might feel if you followed this advice (CAM use) but did not achieve the outcome you hoped for?
	Discuss a reasonable trial period over which an assessment can be made regarding benefits/efficacy of CAM. A symptom diary may	How long would you expect it to take to see a benefit from this CAM?

	help determine whether the CAM is beneficial for the individual patient.	I can see that you hope this CAM will help you/your cancer/symptoms/adverse effects/well-being.
	Explore alternative ways of addressing the patients underlying needs, hopes or fears (especially if there are concerns about potential harms of the CAM)	There are other options we can look at, too. Would you like to hear about them?
7. Advise	Encourage use of CAM that may be beneficial.	I recommend this CAM; The evidence suggests that it could help you.
	Accept use of CAM for which there is no evidence of physical harm or benefit. Support the decision, even though it conflicts with your private view.	We do not know much about this CAM, but it does not seem to be harmful and it may even help you. I respect that this is what you wish to do.
	Discourage use of CAM where there is no good evidence. It will be unsafe or harmful.	I have to be honest with you. I am concerned that this CAM may do you greater harm than good.
	Particularly, discourage use of unproven CAM if it is to be used in place of potentially beneficial treatment, especially potentially curative treatment.	I respect and support your right to make this decision. However, I firmly believe that you have a better chance of a good outcome if you follow this treatment plan. While there is little evidence for us to know if this CAM will be helpful, of course the decision is yours.
	Balance advice with an acknowledgement of the	

		patient's rights for self-determination and autonomy.	
8.	**Summarize**	Summarize main points of discussion and check patient's understanding. Provide websites and other information or resources, e.g. information about supplements, dietary, breathing exercises, yoga, meditation, etc.	We have covered a lot today. Just so that I can check that I have explained things properly, can you summarize what we have discussed? Do you have any further questions or issues you would like to discuss?
9.	**Document**	Document the discussion in the patient's medical record and send a copy to the patient.	I will document what we have discussed today in your medical record and we will send a copy to your secure inbox.
10.	**Follow-up**	Follow-up discussion about CAM if relevant	

Control group: SC

Patients randomized to the control group receive SC i.e. conventional oncology treatment and care, including antineoplastic drugs. SC also involves continuous assessment of performance status, adverse events, symptoms, and their management by specialist doctors and nurses. The patients are given a pamphlet describing and referring to a website, www.kabcancer.dk. Based on systematic reviews, this website presents research-based information on effects and outcomes of specific CAM interventions i.e. acupuncture, antioxidant supplements, mindfulness, herbs, massage etc. [35].

No concomitant medications or consultations are prohibited during the study.

Primary outcome measure

The primary outcome measure is the difference in level of patient reported quality of life, specifically with regard to emotional well-being, between the two groups eight weeks^{t1} after enrollment. The patient reported data will be registered according to the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire computerized adaptive test (EORTC QLQ CAT Core). The EORTC QLQ CAT core is a translated and validated instrument, which encompasses 15 domains with pools of validated questions. Within each pool of questions, the EORTC CAT Core selects and presents the question that is the most informative for the individual patient. The instrument lists questions assessing quality of life, including functional scales, symptom scales, global health status, and psychosocial scales [36].

Secondary outcome measures

The secondary outcome measure is the change from baseline to post intervention 8^{t1}, 12^{t2} and 24^{t3} weeks after enrollment. Difference between the two groups will be assessed in the following outcomes.

- Patient reported anxiety and depression evaluated by the Hospital Anxiety and Depression Scale (HADS). HADS is a translated and validated self-assessment questionnaire detecting states of anxiety and depression in the setting of hospital outpatient clinics [37].
- Patient reported level of top concern evaluated by Measure Yourself Concerns and Wellbeing (MYCaW). MYCaW is an individualized questionnaire

scoring patients concerns, problems and well-being and collecting qualitative data about other major events in a patient's life and what has been most important to the patient [38].

- Patient-reported level of decision regret regarding conventional oncology treatment evaluated by the Decision Regret Scale (DRS). The DRS is a validated measurement tool measuring the distress or remorse after a health care decision [39].
- Patient-reported quality of life 12 and 24 weeks after enrollment evaluated by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ CAT Core) [36].

Overall survival will be measured 12 months after enrollment of last patient.

Process measures

Variables likely to mediate the effect of OD-CAM will be measured twice during follow-up (at baseline^{-t1} and 24^{t3} weeks):

- Attitude of CAM
- Use of CAM including type

Flowchart and participant timeline are presented in Table 2 and Figure 1, respectively. All questionnaires are administered electronically. If questionnaires are not completed within 2 weeks, a reminder is sent.

Table 2. Participant timeline

	STUDY PERIOD				
	Enrolment	**Allocation**	**Post-allocation**		
TIMEPOINT	$-t_1$	**0**	t_1 *8 weeks*	t_2 *12 weeks*	t_3 *24 weeks*
ENROLLMENT					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS					
SC+OD-CAM			◆——	——	——◆
SC			◆——	——	——◆
ASSESSMENTS					
Baseline variables:					
Demographic data	X				
QoL	X				
Anxiety and depression	X				
Top concerns	X				
Decision regret	X				
Attitude and use of CAM	X				
Outcome variables:					
QoL					
Anxiety and depression			X		
Top concerns			X	X	X

Decision regret			X X	X X X	X X X
Mediators: Attitude and use of CAM					X

Data management

Cooperation and a license agreement have been established with the OPEN organization (Odense Patient data Explorative Network). All sensitive data will be registered and stored in OPEN Analyze and handled in REDCap, a mature, secure web application for building and managing online surveys and databases. REDCap provides logging at the transaction level and may therefore store and process any person identifiable data. Thus, congruent with guidelines, sensitive data about the patients are stored and handled securely [40].

STATA software (Texas, USA) will be used as a platform for statistical analysis. Since STATA only provides logging at the file level, participant data will be pseudonymized by assigning a unique ID number to each participant. The list of ID numbers and the pertaining key will be kept separately. Information on user and time of data processing in STATA will be logged.

Only persons involved in the project are allowed to access data. In accordance with the license agreement principal investigator (Mette Stie) controls access and rights and the OPEN data manager provides the access.

Research nurses in the clinical trial unit will only have the right to enter data into REDCap. Data collected on paper (baseline data) will be registered in REDCap. The

electronic questionnaires are completed by the patients directly in REDCap, which promotes data quality.

Statistical analysis plan

Sample size

The sample size is calculated on the basis of the primary endpoint. A 10-point difference or more in the quality-of-life EORTC QLQ CAT Core scale from baseline to 8 weeks between the two study groups is considered of clinical importance. We plan a randomized controlled study of a continuous response variable in independent control and experimental subjects with one control per experimental subject. In a previous study, the response within each subject group was normally distributed with a standard deviation of 24.2. If the true difference in the experimental and control means is 10, the number of subjects required in each group is 93 to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.8. The type I error probability associated with this test of the null hypothesis is 0.05. With an expected loss of 10%, the total number of patients to be enrolled is 207.

Statistical methods

The intervention arm (OD-CAM) will be compared against the control arm (SC plus referral to www.kabcancer.dk) in all primary analyses. Demographic data will be presented as counts (n) and proportions (%), respectively, means and standard deviations (SD) with 95% confidence intervals (CI). Chi-square test or a Fisher exact test will be applied where appropriate to detect differences between the two groups in relation to quality of life. The EORTC QLQ CAT Core, HADS scores, DRS, and

MYCaW will be reported as means and standard deviations compared between the two groups by using Student's t-test or Mann Whitney's U test, depending on normality of the data checked by quantile-quantile plots.

P-values will be reported to three decimal places with p-values less than 0.001 reported as <0.001. Two-sided p-values with a 0.10 level of significance will be used for all tests. Kaplan-Meier survival analysis will be applied to detect potential difference in overall survival between the two group. A professional academic, statistician blinded to the study group assignment will conduct all analyses. For potential subgroup analyses, appropriate regression methods will be applied e.g. in case of a great variety in number of OD-CAM sessions

Patient and public involvement

The Patient and Relative Council Board at Lillebaelt Hospital initiate the CAMONCO 1 and 2 studies. Before submission, this research protocol was developed and reviewed by the CAMONCO steering group, a joint initiative of patients with cancer, health professionals and staff representing medical oncology, oncology nursing and nurse managers. Furthermore, Danish Cancer Society is represented in the CAMONCO steering group. Patients in the CAMONCO steering group were in particular involved in development of the intervention OD-CAM and time required to participate in the study. Also, patients` priorities, experiences and preferences informed some of the outcome measures (EORTC-CAT core and MYCaW). The steering group will continuously provide feedback on interim findings and advise on dissemination of results and output of the study. Patients from the steering group are pivotal partners in the dissemination of the CAMONCO 1 and 2

studies to relevant stakeholders.

Ethics and disseminations

According to the Committee on Health Research Ethics for Southern Denmark, ethics approval of this study is not required (S-20202000-5, 20/1019). The Region of Southern Denmark (Journal no. 20/11100) approved the storing and handling of data. The procedures in this study adhere to the principals of the Declaration of Helsinki. Thus, patients are informed about the purpose of the study, including the right to withdraw, the guarantee of anonymity, and the confidentiality of the data. Trained nurses or study nurses will introduce and discuss the trial with the patients. If needed, patients will be able to have an informed discussion about the trial with the principal investigator. The trained nurses or study nurses will obtain written consent from patients willing to participate in the trial (see patient consent form in supplementary file). Subsequently, demographic data and questionnaires regarding patients' quality of life, depression and anxiety, concerns and wellbeing, and decision regrets will be collected, preserved and shared only by researchers involved in this trial.

It is estimated that the study does not involve any risk to the patients, and the potential benefits clearly outweigh the theoretical risks involved in participating in open dialogue about CAM and completing questionnaires.

The results of the study, whether positive, negative or inconclusive, will be disseminated through open-access, peer-reviewed publications, stake-holder-reporting and presentations at relevant conferences.

Discussion

The need for OD-CAM as an integral part of oncology care becomes increasingly urgent with the increasing number of patients using CAM as an adjunct to conventional oncology treatment. To the best of our knowledge, this is the first randomized controlled trial that aims to evaluate the efficacy of OD-CAM integrated in conventional oncology care versus standard care in patients undergoing anti-cancer treatment, by the EORTC QLQ CAT Core, the HADS, the MYCaW and the DRS questionnaires. The current study will shed light on the effect of OD-CAM on patients receiving outpatient oncology treatment for cancer and provide foundation for guidelines on how to meet patients` needs for guidance in safe and health promoting use of CAM. It will also add to the evidence-based knowledge on communication about CAM between patients and health professionals in clinical practice. Only few studies have exclusively explored the effects OD-CAM integrated in conventional oncology care [26]. Most of them include both open dialogue and the provision of CAM and mainly assess patient satisfaction. According to our knowledge, only one study other than our previous trial (CAMONCO 1), has investigated the effects of open dialogue about CAM on patients' symptoms, quality of life and well-being [33]. The present CAMONCO 2 study will therefore be an important contribution to the sparse knowledge on the issues as integrated in conventional oncology care.

Strengths and limitations

One limitation of the present study may be that since little is known about the effects of OD-CAM, the pragmatic choice of including patients with different cancer

diagnoses and prognoses may be too broad. On the other hand, these patients have much in common including the need for self-care, self-control, and empowerment, which are some of the main reasons for using CAM [41-43]. The randomization secures the even distribution of different diagnoses and prognoses. Only the researchers are blinded to the allocation, which is a limitation but necessary due to the nature of the intervention. The complexity of the intervention also makes it difficult to determine the potential effects, but the same nurse-specialist conducts the OD-CAM throughout the study, which secures a homogenous intervention.

The prospective, randomized design with a control group and the use of validated patient-reported questionnaires is a strength of the study. Strengths also include the use of the EORTC QLQ CAT CORE questionnaire, it increases measurement precision, flexibility, question relevance to the individual patients, and reduces respondent burden.

Study status

The first participant was enrolled on May 11, 2020. 181 patients were enrolled at the time of preparation of this manuscript.

Contributors

All authors, Mette Stie (MS), Charlotte Delmar (CD), Birgitte Nørgaard (BN), and Lars Henrik Jensen (LHJ), have contributed to the study planning, conception and design. MS and LHJ perform material preparation, data collection and analysis. MS wrote the first draft of the manuscript and CD, BN and LHJ revised it critically for

important intellectual content. MS, CD, BN and LHJ have approved publication of the final version and agree to be accountable for all aspects of the work.

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Competing interests

The authors declare that they have no competing interest.

Consent for publication

Not applicable.

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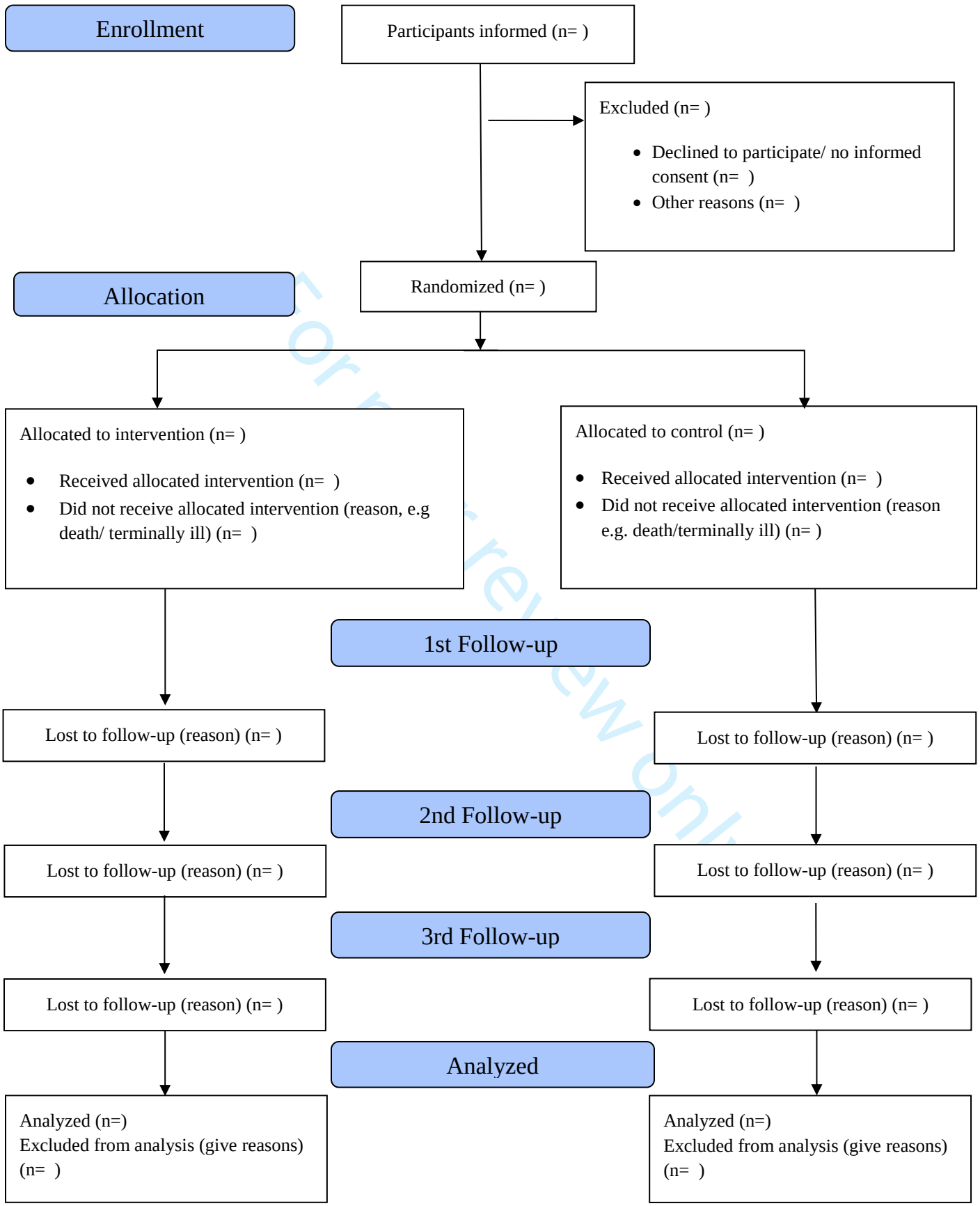
Figure Titles

Figure 1. Study flowchart

Figure 1 Flow chart



Deltagerinformation og samtykkeerklæring ved deltagelse i et videnskabeligt projekt

Effekten af åben dialog om komplementær og alternativ behandling integreret i kræftbehandlingen. Patientoplevet livskvalitet og velvære

Engelsk titel:
The efficacy of open dialogue about complementary alternative medicine integrated in conventional oncology care. Patient reported quality of life and well-being

Version 1
2. marts 2020

Deltagerinformation

Vi ønsker at fremme åben dialog mellem patienter og sundhedsprofessionelle om komplementær og alternativ behandling, når patienter har et behandlingsforløb i Onkologisk Afdeling. Det alternative kan f.eks. bestå af kosttilskud, akupunktur, massage mm. De, der bedst kan hjælpe os, er patienter som dig, der er i kræftbehandling. Derfor vil vi spørge, om du vil deltage i et videnskabeligt forsøg, der udføres på Onkologisk Afdeling.

Før du beslutter, om du vil deltage i forsøget, skal du fuldt ud forstå, hvad det går ud på. Vi vil derfor bede dig om at læse denne deltagerinformation igennem. Ved din næste samtale eller behandling i Onkologisk Ambulatorium vil forsøget blive uddybet og du kan stille spørgsmål. Du er velkommen til at tage et familiemedlem, en ven eller en bekendt med til samtalen. Herefter har du ret til betænkningstid på mindst et døgn.

Sammen med denne deltagerinformation har du også fået udleveret folderen "Før du beslutter dig", som vi opfordrer dig til at læse. Her kan du få yderligere oplysninger om deltagelse i forsøg.

Det er frivilligt at deltage og du kan når som helst og uden grund trække dit samtykke tilbage. Det vil på ingen måde få indflydelse på din videre behandling.

Hvis du beslutter dig for at deltage i forsøget, vil vi bede dig om at underskrive samtykkeerklæringen vedhæftet denne information. Hvis du ikke ønsker at deltage, håber vi, du vil udfylde sidste side.

Baggrund for projektet

Mange patienter med kræft anvender såkaldt komplementær og alternativ behandling (KAB) som et supplement til kemoterapi eller immunterapi. I nogle tilfælde er disse behandlinger ikke forenelige, hvilket kan betyde, at man enten ikke får gavn af kemoterapien og immunterapien eller, at man får unødige bivirkninger. På den anden side kan visse former for KAB øge livskvaliteten og velværet hos patienter med kræft. Derfor er det vigtigt, at patienter og sundhedsprofessionelle taler åbent med hinanden om både fordele og ulemper ved KAB som et supplement til kemoterapi eller immunterapi.

Baseret på vores tidligere, lignende projekt tyder det på, at åben dialog om KAB kan forbedre patientens livskvalitet og velvære. Denne undersøgelse skal derfor vise, om samtaler om KAB som en integreret del af kræftbehandlingen kan forbedre patientens livskvalitet og velvære og bidrage til, at patienten er tilfreds med sit valg om at modtage kræftbehandling.

Hvad går projektet ud på?

Vi inviterer 207 patienter til at deltage i undersøgelsen. Halvdelen tilbydes en samtale om KAB med en specialuddannet sygeplejerske. De patienter, der ikke tilbydes samtale om komplementær og alternativ behandling, følger Onkologisk Afdelings vanlige forløb, der består af samtaler om kemoterapi og/eller immunterapi samt henvisning til en hjemmeside om komplementær og alternativ behandling (www.KABcancer.dk). Udvælgelsen foregår ved computerbaseret lodtrækning.

Få dage efter underskrivelse af samtykkeerklæringen får man besked på, om man er blevet tildelt en samtale om KAB.

Samtalen foregår i starten af behandlingsforløbet i Onkologisk Afdeling og varer 1 time. Den tager udgangspunkt i patientens værdier, ønsker og præferencer med hensyn til KAB og indeholder råd og vejledning i forhold hertil. Hvis der er behov for det, tilbydes en opfølgende samtale.

For at kunne undersøge effekten af disse samtaler vil vi bede dig om at udfylde et spørgeskema 4 gange i løbet af behandlingsforløbet. Det første skema modtager du på papir i forbindelse med tilmeldingen til forsøget. De næste får du i eBoks 8, 12 og 24 uger senere til udfyldelse elektronisk.

Hvad betyder forsøget for dig selv eller andre?

Hvis du bliver udvalgt til at deltage i en samtale om KAB, er det muligt, at du vil drage nytte deraf. Resultaterne af forsøget forventes dog primært at være nyttige i forhold til fremtidige patienter med kræft.

Eventuelle bivirkninger, risici eller ulemper

Du udsættes ikke for øget risiko eller ubehag. Det kan føles som en ulempe ved forsøget, at du skal bruge tid på at besvare spørgeskemaer og at du muligvis vil skulle møde en ekstra gang i Onkologisk Ambulatorium.

Hvem kan få oplysninger?

Alle oplysninger om dig i dette projekt opbevares fortroligt i henhold til dansk lovgivning (databeskyttelsesloven og databeskyttelsesforordningen). Personale, der er involveret i projektet, vil få adgang til oplysningerne i indtil 5 år efter forsøgets afslutning. Tavshedspligt er gældende for alt personale, og din identitet bliver ikke afsløret, når vi offentliggør resultaterne af projektet. Vi registrerer en række oplysninger om din sygdom fra din elektroniske patientjournal, men kun de oplysninger, der er nødvendige for at opgøre forsøgsresultaterne.

Projektet gennemføres i et samarbejde mellem Onkologisk Afdeling, Vejle Sygehus og Syddansk Universitet. Resultaterne af undersøgelsen forventes at kunne gøres op i år 2021 og vil i anonymiseret form blive søgt offentliggjort i et internationalt, videnskabeligt tidsskrift og være tilgængelige på www.ClinicalTrials.gov. Du er også velkommen til at kontakte undertegnede til den tid for at få et uddrag af resultaterne.

Godkendelse og økonomi

Patient- og Pårørenderådet ved Vejle Sygehus har taget initiativ til undersøgelsen, som er godkendt af Region Syddanmark. Studiet finansieres delvist af Fondation Idella. Øvrige fonde vil blive søgt om midler til aflønning af projektsygeplejerske og statistiker.

Vi håber, at du med denne information har fået tilstrækkeligt indblik i, hvad det vil sige at deltage i forsøget, og at du føler dig rustet til at tage beslutning om din eventuelle deltagelse.

Med venlig hilsen

Lars Henrik Jensen
Klinisk lektor, overlæge, PhD
Onkologisk Afdeling
Vejle Sygehus

Mette Stie
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Tlf.: 7940 6060

Patientens kopi

Samtykkeerklæring

Effekten af åben dialog om komplementær og alternativ behandling integreret i kræftbehandlingen. Patientoplevet livskvalitet og velvære. CAMONCO 2
(The efficacy of open dialogue about complementary alternative medicine integrated in conventional oncology care. Patient reported quality of life and well-being, CAMONCO 2)

Erklæring fra forsøgsdeltageren

Jeg har fået skriftlig og mundtlig information og jeg ved nok om formål, metode, fordele og ulemper til at sige ja til at deltage.

Jeg ved, at det er frivilligt at deltage, og at jeg altid kan trække mit samtykke tilbage uden at miste mine nuværende eller fremtidige rettigheder til behandling.

Jeg giver samtykke til at deltage i forskningsprojektet og til at forskningsgruppen må hente oplysninger i min journal om mit behandlingsforløb i Onkologisk Afdeling til brug i projektet.

Jeg har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Patient navn: _____
BLOKBOGSTAVER

Jeg ønsker at besvare spørgeskemaer elektronisk (sæt X) ___JA ___NEJ

Mailadresse _____

Dato og patientunderskrift: _____
Dato Underskrift

Erklæring fra den informerende sygeplejerske/læge

Jeg erklærer, at forsøgsdeltageren har modtaget mundtlig og skriftlig information om forsøget og har haft mulighed for at stille spørgsmål til mig. Efter min overbevisning er der givet tilstrækkelig information til, at der kan træffes beslutning om deltagelse i forsøget.

Informerende sygeplejerske/læge: _____
BLOKBOGSTAVER

Dato og underskrift, informerende sygeplejerske/læge:

_____
Dato Underskrift

Sygeplejerskens/lægens kopi

Samtykkeerklæring

Effekten af åben dialog om komplementær og alternativ behandling integreret i kræftbehandlingen. Patientoplevet livskvalitet og velvære, CAMONCO 2
(The efficacy of open dialogue about complementary alternative medicine integrated in conventional oncology care. Patient reported quality of life and well-being, CAMONCO 2)

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Jeg giver samtykke til at deltage i forskningsprojektet og til at forskningsgruppen må hente oplysninger i min journal om mit behandlingsforløb i Onkologisk Afdeling til brug i projektet.

Jeg har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Patient navn: _____
BLOKBOGSTAVER

Jeg ønsker at besvare spørgeskemaer elektronisk (sæt X) ___JA ___NEJ

Mailadresse _____

Dato og patientunderskrift: _____
Dato Underskrift

Erklæring fra den informerende sygeplejerske/læge

Jeg erklærer, at forsøgsdeltageren har modtaget mundtlig og skriftlig information om forsøget og har haft mulighed for at stille spørgsmål til mig. Efter min overbevisning er der givet tilstrækkelig information til, at der kan træffes beslutning om deltagelse i forsøget.

Informerende sygeplejerske/læge: _____
BLOKBOGSTAVER

Dato og underskrift, informerende sygeplejerske/læge:

_____
Dato Underskrift

Udfyldes af Forskningsenheden

Patientnummer ☐☐☐ **Patient-initialer** ☐☐☐

Jeg ønsker ikke at deltage

Tak fordi du tog dig tid til at blive informeret og forholde dig til projektet. Din beslutning om ikke at deltage, får på ingen måde indflydelse på din videre behandling og pleje.

Vi vil dog sætte pris på at få dine svar på nedenstående få spørgsmål.

1) Hvad er dit køn? (sæt x) ____Mand ____Kvinde

2) Hvad er din fødselsdato og år?_____

3) Hvilken type kræft er du i behandling for (sæt X)

- O Brystkræft
- O Prostatakræft
- O Lungekræft
- O Tarmkræft
- O Æggestokkræft
- O Livmoderkræft
- O Bugspytkirtelkræft

4) Hvad er målet med behandlingen? (sæt x) ____Helbredelse ____Lindring

Mange tak for din besvarelse.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym : **Efficacy of open dialogue about complementary and alternative medicine compared with standard care in improving quality of life in patients undergoing conventional oncology treatment (CAMONCO 2): protocol for a randomized controlled trial**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry: **Trial registration: ClinicalTrails.gov, Identifier: NCT04299451 March 2020.**
	2b	All items from the World Health Organization Trial Registration Data Set **All item are included in the protocol and the manuscript: Primary registry and trial identifying number, date of registration, primary sponsor, contact information, title, country, health conditions and problems studied, interventions, key inclusion criteria, study type, date of first inclusion, sample size, recruitment status, primary and secondary outcomes.**
Protocol version	3	Date and version identifier: **OK**
Funding	4	Sources and types of financial, material, and other support: **Declarations - *Funding* page 15**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **Declarations- *Author contributions* page 15**
	5b	Name and contact information for the trial sponsor: **Title page**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities. **Funding page 26**

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) **N/A**
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **Described in the Background section at page 3**
	6b	Explanation for choice of comparators **Background page 3-4**
Objectives	7	Specific objectives or hypotheses **Aim page 5**
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **Design page 5**
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **Setting page 5-6**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **Participants page 6**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **Interventions page 7-8**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease**) It is estimated that the study does not involve any risk to the patients, and the potential benefits clearly outweigh the theoretical risks involved in participating in open dialogue about CAM and completing questionnaires – see Ethical considerations page 12**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **In the Outcome measures page 18**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **page 16**

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **Primary and secondary outcome measures are describe at page 9-10. Clinical relevance is described in Design page 5**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) **see Figure 1 and Table 2**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **Statistical plan page 11**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **Recruitment page 6**

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions. **Upon signed consent and completed baseline questionnaires randomization is performed by the clinical trial unit using OPEN Randomize (https://open.rsyd.dk/), an online central randomization service. Page 7**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **–do- page 7**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions**. Recuitment procedures and allocation is described in the recruitment and the randomization section p. 6 and 7, respectively.**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how. **The principal investigator is blinded to the allocation –see Blinding section page 7**

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **n/a**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **Questionnaires are described in the Primary outcome and secondary outcome section page 9-10 , Data management page 10-11**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **Data management page 10-11**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **Data management procedures are described in the protocol and in the Data management section page 10-11**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **Statistical plan page 11-12**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **N/A**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **N/A**
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **N/A**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **N/A**

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **N/A**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **N/A**

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval Declarations. **See Ethics approval page 14**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **n/a**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **See Ethical considerations page 12**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **N/A**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial **See Data management page 10 and Ethical considerations page 12**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site. **No competing interest – page 26**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators. **Only researchers involved in this project will have access to final trial dataset. – Data management section page 20**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **N/A**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **The results of the study, whether positive, negative or inconclusive, will be published in a relevant journal with authorship following the Vancouver rules. Ethics and dissemination section page 23**

	31b	Authorship eligibility guidelines and any intended use of professional writers **N/A**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **N/A**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **Informed consent p. 23 and upload as supplementary material**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.